Specification

The specification has been objected to for containing embedded hyperlink and/or other form of browser-executable code. The foregoing amendment, which deleted all embedded hyperlinks, is believed to overcome this objection.

Claim Rejections - 35 U.S.C. § 112

(1) Claims 39-51 have been rejected under 35 U.S.C. § 112, second paragraph as "indefinite" in their recitation of "extracellular domain" with reference to the PRO211 polypeptides. The Examiner noted that PRO211 is a soluble protein, which does not have an extracellular domain.

Claims 47 and 48 have been cancelled. Upon entry of the foregoing amendment, the remaining claims no longer contain a reference to an extracellular domain. Accordingly, the withdrawal of the present rejection would be in order.

(2) Claims 39-43 and 50-51 were rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement for the genus claimed. The Examiner acknowledged, however, that enablement was present for isolated polypeptides that have at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO: 2, or the mature form thereof, and inhibit VEGF stimulated proliferation of adrenal cortical capillary endothelial cells.

As noted before, Applicants rely on the gene amplification data provided in Example 92 to establish a specific, substantial and credible asserted utility for the PRO211 polypeptides. Accordingly, the genus claims, as amended, recite that the claimed polypeptides are associated with the formation or growth of lung or colon tumor.

Gene amplification is an essential mechanism for oncogene activation. It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis. As described in Example 92 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8 (pages 230-234 of the specification), including primary lung cancers and colon cancers of the type and stage indicated in Table 8 (page 227). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 222, lines 34-36).

Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 9. As explained in the passage bridging pages 222 and 223, the results of TaqMan™ PCR are reported in ΔCt units. One unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold, etc. amplification. PRO211 showed 2-3 fold gene amplification in a number of lung and colon tumors.

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan™ real-time PCR method described in Example 92 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results set forth in Table 9 one of ordinary skill would find it credible that PRO211 is a diagnostic marker of human lung and colon cancer.

Since, in addition to the percent sequence identity figures, the claims now recite that the claimed polypeptides are associated with the formation or growth of lung or colon tumor, the invention as claimed in claims 39-43 and 50-51 is fully enabled. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(3) Claims 39-43 and 50-1 have been rejected under 35 U.S.C. §112, first paragraph for alleged lack of sufficient written description. The Examiner noted that the claims directed to polypeptides having 80%, 85%, 90%, 95%, or 99% sequence identity with the polypeptide of SEQ D NO: 2 did not require that the polypeptides possess any biological activity.

The claims have been amended to recite a biological activity. Applicants submit that at the effective filing date of the present application a person skilled in the art would have reasonably recognized that Applicants were in the possession of the invention now claimed, within the full scope of claims pending. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Attached hereto is a marked-up version of the amendments made to the specification and claims, entitled "**Version with markings to show changes made.**"

All claims are believed in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No: 39780-1618P2C5). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Dated: March 14, 2003

By: _____
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Version with markings to show changes made

In the Specification:

The original title has been canceled, and replaced with the following new title: ----PRO211 polypeptides.--

The paragraph, beginning at page 69, line 6, has been amended as follows:

--Percent amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). [The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov.] NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.--

The paragraph, beginning at page 71, line 26, has been amended as follows:

--Percent nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). [The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov.] NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.--

The paragraph beginning at page 147, line 27, has been amended as follows:

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public databases (e.g., Dayhoff, GenBank), and proprietary databases (e.g. LIFESEQ^{TM}, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altschul, and Gish, Methods in

Enzymology 266: 460-80 (1996)[; http://blast.wustl/edu/blast/README.html]) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons with a Blast score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

The paragraph, beginning at page 154, line 14 has been amended as follows:

--The EST sequence accession number AF007268, a murine fibroblast growth factor (FGF-15) was used to search various public EST databases (e.g., GenBank, Dayhoff, etc.) The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)[; http://blast.wustl/edu/blast/README.html]] as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. The search resulted in a hit with GenBank EST AA220994, which has been identified as stratagene NT2 neuronal precursor 937230.--

The paragraph beginning at page 167, line 30, has been amended as follows:

--The extracellular domain (ECD) sequences (including the secretion signal, if any) of from about 950 known secreted proteins from the Swiss-Prot public protein database were used to search expressed sequence tag (EST) databases. The EST databases included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequence. Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington[; http://bozeman.mbt.washington.edu/phrap.docs/phrap.html]).

The paragraph beginning at page 178, line 14, has been amended as follows:

--The extracellular domain (ECD) sequences (including the secretion signal, if any) of from about 950 known secreted proteins from the Swiss-Prot public protein database were used to search expressed sequence tag (EST) databases. The EST databases included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequence. Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington[; http://bozeman.mbt.washington.edu/phrap.docs/phrap.html]).--

In the Claims:

Claims 47 and 48 have been cancelled.

Claims 39-44 and 49 have been amended as follows:

39. (Once amended) An isolated polypeptide having at least 80% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2);

(b) the amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2), lacking its associated signal peptide; or,

(c) [the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2);

(d) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), lacking its associated signal peptide; or

(e)] the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number [2209258] 209258,

wherein said polypeptide is associated with the formation or growth of lung or colon tumor.

40. (Once amended) The isolated polypeptide of Claim 39 having at least 85% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2);

(b) the amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2), lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2);

(d) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), lacking its associated signal peptide; or

(e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number [2209258] 209258;

wherein said polypeptide is associated with the formation or growth of lung or colon tumor.

41. (Once amended) (Once amended) The isolated polypeptide of Claim 39 having at least 90% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2);

(b) the amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2), lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2);

(d) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), lacking its associated signal peptide; or

(e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number [2209258] 209258;

wherein said polypeptide is associated with the formation or growth of lung or colon tumor..

42. (Once amended) The isolated polypeptide of Claim 39 having at least 95% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2);

(b) the amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2), lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2);

(d) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), lacking its associated signal peptide; or

(e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number [2209258] 209258;

wherein said polypeptide is associated with the formation or growth of lung or colon tumor.

43. (Once amended) The isolated polypeptide of Claim 39 having at least 99% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2);

(b) the amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2), lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2);

(d) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), lacking its associated signal peptide; or

(e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number [2209258] 209258;

wherein said polypeptide is associated with the formation or growth of lung or colon tumor.

44. (Once amended) An isolated polypeptide comprising:

(a) the amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2);

(b) the amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2), lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2);

(d) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), lacking its associated signal peptide; or

(e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number [2209258] 209258.

49. (Once amended) The isolated polypeptide of claim 44 comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number [2209258] 209258.